REMARKS

Claim Amendments

Claims 1 is amended. The amendment is not to be construed as an admission regarding the patentability of the full scope of the invention, but is merely to expedite the prosecution of the present application. Support for the claimed heterocycles can be found, for example, on page 6, last two lines, and page 7, lines 1-3, 5, 8-10, 13-15 and 18. Support for the amendment to R^4 and R^5 together can be found, for example, on page 7, last paragraph. An amendment is made to the form of claim 5 and 15 whereby no change in scope is achieved. Claim 15 now specifically points out that inhibiting neuronal NDS achieves the treatment of a neurodegenerative disease. A typographical obvious error is corrected in claim 12. Claims 4 is cancelled without prejudice or disclaimer. Claim 16 is rewritten in independent form, as only an objection was issued with respect to this claim.

The Section 112, first paragraph rejections

The Office Action alleges that the term "neurodegenerative diseases" in claim 9 is indefinite because it is broad. The breadth of the claim has nothing to do with whether it is definite or not. One of ordianry skill in the art understands what is meant by the term, as it has a well recognized and delineated meaning. A broad claim is not indefinite if the breadth of the claim is ascertainable. See *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971. Furthermore, the specification provides ample guidance through examples of specific diseases, which one of ordinary skill in the art can use to ascertain the meaning of the term.

The Office Action further alleges that claims 12-14 were not enabled primarily because the applicants did not test the effect of the compounds on the claimed diseases. However the law does not require that a patent applicant test pharmaceutically active compounds on patients. See *In re Brana*, 51 F.3d 1560 (Fed. Cir. 03/30/1995).

In *Brana*, the court said that it is its firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and

development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The Office Action alleges that the level of predictability in the art is nonexistent since the applicant does not test the effect of these compounds on the diseases claimed. The level of predictability in the art has nothing to do with the tests furnished by an applicant. The Office Action next alleges that the amount of direction provided is poor because the applicant does not test any compounds for their effect on the diseases claimed. The law does not require that an applicant test the compounds on claimed diseases. The allegation that undue experimentation would be required to make the use of the invention is merely a conclusion without setting forth any underlying facts. The allegation merely recites three other Wands factors to support the conclusion, two of which was just discussed, i.e., level of predictability in the art and amount of direction provided, each supported by the reasoning that applicants did not test the compounds on the diseases claimed. Such a requirement however is not founded in law.

Primarily, a disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 03/30/1995)

The Examiner has given no reason for doubt of the objective truth of the statements in the application, which must be relied on for enabling support. The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of Section 112 requires nothing more than objective enablement, how such a teaching is set forth, either by use of the illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971).

Applicants respectfully submit that it is the initial burden of the PTO to establish a reason to doubt the truth of the statements presented in the specification concerning utility.

See, e.g., *In re Marzocchi et al.*, supra) ("...it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure....") The only reason alleged by the Office Action, other than mere conclusions, was that applicants did not test the compound on diseases claimed, which is not a proper reason.

Merely because it is asserted that a specific example of treating a disease is not presented in the specification, one of ordinary skill in the art would not doubt the truth of the statements concerning the treatability of such diseases. MPEP § 2164.02 states that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. The nature of the invention and the state of the prior art further demonstrate that Applicants' specification provides sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention. The specification teaches diseases which are treatable by the claimed compounds. The specification further teaches, for example, in the paragraph spanning from page 16-17, doses and preferred doses to be administered to a patient to treat the claimed diseases.

Thus the claims are enabled.

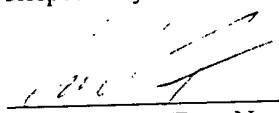
Claim 15 was amended to specifically points out that inhibiting neuronal NDS achieves the treatment of a neurodegenerative disease. All arguments from above are incorporated herein with respect to the rejection of the breadth of the "neurodegenerative disease" term.

Entry and consideration of the amendments and remarks are respectfully requested. Applicants believe that the claims are in a form ready for allowance, but if there are any residual issues which can be expeditiously resolved by a telephone conference, the Examiner is courteously invited to telephone Counsel at the number indicated below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To Show Changes Made**".

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Date: June 12, 2002

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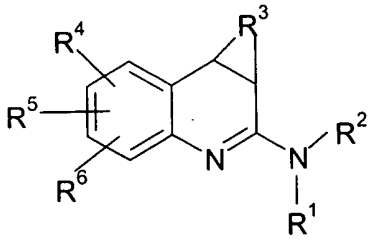
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

The claims have been amended as follows:

1. A compound of formula I,



(I)

wherein

R^1 and R^2 are, independently of one another, hydrogen, C_{1-6} alkyl, OR^7, NR^7R^8, CN, acyl, CO_2R^9, $CONR^7R^8$ or $CSNR^7R^8$,

R^3 is a saturated or unsaturated C_{1-5} alkylene radical, which is optionally substituted in 1 to 4 places with OR^7, $NR^{11}R^{12}$ or C_{1-4} alkyl and in which 1 or 2 CH_2 groups are optionally and independently replaced by O, $S(O)_n$, NR^8, =N- or carbonyl, and which are optionally bridged with a methano, ethano or propano group,

R^4 is C_{1-4} alkyl, substituted with $NR^{14}R^{15}$, ~~or~~

R^4 and R^5 optionally together with 2 adjacent carbon atoms form a <u>C_3- C_4 alkylene moiety optionally substituted in one or two places with $NR^{14}R^{15}$,</u> ~~five- or six-membered carbocyclic compound, which is optionally substituted with $NR^{14}R^{15}$;~~

R^5 and R^6 are, independently of one another, Hydrogen, halogen, OR^7, C_{1-4} alkyl, CF_3, or OCF_3,

R^7, R^{18} and R^{19} are, independently of one another, Hydrogen, C_{1-6} alkyl or C_{6-10} aryl, which optionally is substituted with halogen or C_{1-4} alkyl,

R^8, R^{11}

and R^{12} are, independently of one another, Hydrogen, C_{1-6} alkyl, C_{6-10} aryl, which optionally is substituted with halogen or C_{1-4} alkyl, COR^{10}, CO_2R^{10}, $CONR^{18}R^{19}$ or $CSNR^{18}R^{19}$,

R^9, R^{10} and R^{20} are, independently of one another, C_{1-6} alkyl or C_{6-10} aryl, which optionally is substituted with halogen or C_{1-4} alkyl,

R^{14} and R^{15} are, independently of one another, Hydrogen, CO_2R^{20} or C_{1-6} alkyl, which optionally is substituted with halogen, hydroxy, C_{1-4} alkoxy, nitro, amino, C_{1-6} alkyl, trifluoromethyl, carboxyl, cyano, carboxamido, C_{3-7} cycloalkyl, indanyl, 1,2,3,4-tetrahydronaphthyl, C_{6-10} aryl, ~~5- or 6-membered heteroaryl with 1-4 nitrogen, oxygen or sulfur atoms, which are optionally annelated with benzene, whereby~~ wherein the aryl radical ~~and the heteroaryl radical are~~ is optionally substituted with halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, CF_3, NO_2, NH_2, $N(C_{1-4}$ alkyl$)_2$ or carboxyl, or

R^{14} and R^{15} optionally together with the nitrogen atom ~~of R^4 or R^4 and R^5 together~~ form ~~a 5- to 7-membered saturated heterocycle, which optionally comprises an oxygen, sulphur or another nitrogen atom and are optionally substituted with C_{1-4} alkyl, phenyl, benzyl or benzoyl radical which is optionally substituted with halogen, or an unsaturated 5-membered heterocycle, which optionally contains 1-3 N atoms and is optionally substituted with phenyl, C_{1-4} alkyl, halogen or CH_2-OH,~~ imidazole, indole, isooxazole, isothiazole, furan, oxadiazole, oxazole, pyrazine, pyridazine, pyrimidine, pyridine, pyrazole, pyrrole, tetrazole, thiazole, triazole, thiophene, thiadiazole, benzimidazole, benzofuran, benzoxazole, isoquinoline, quinoline, furanyl, thienyl, piperidine, pyrrolidine, morpholine, thiomorpholine, hexahydroazepine, piperazine, N-methyl-piperazine, 2,6-dimethylmorpholine, phenylpiperazine, 4-(4-fluorobenzoyl)-piperidine, or indazole, and

n is 0, 1 or 2,

or a tautomeric ~~and~~ or isomeric ~~forms and salts~~ form or a salt of a compound of formula I.

Please cancel claim 4 without prejudice or disclaimer.

5. A compound according to claim 1, wherein said compound is ~~selected from~~,

a) 4-Amino-7-(N-tert-butyloxycarbonyl-3-chlorobenzylamino)methyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline;

b) 4-amino-7-(3-chlorobenzylamino)methyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline dihydrochloride;

c) 4-amino-7-(N-tert-butoxycarbonyl-3-chlorobenzylamino)ethyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline;

d) 4-amino-7-(3-chlorobenzylamino)ethyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline dihydrochloride ;

e) 4-amino-7-(N-tert-butoxycarbonyl-3-chlorobenzylamino)-1,2,3,3a,7,8,9,10b-octahydro-dicylopenta[c,g]quinoline;

f) 4-amino-7-(3-chlorobenzylamino)-1,2,3,3a,7,8,9,10b-octahydro-dicyclopenta[c,g]quinoline;

g) 4-amino-7-[1-(N-tert-butoxycarbonyl-3-chlorobenzylamino)propyl]-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline;

h) 4-amino-7-[1-(3-chlorobenzylamino)propyl]-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline;

i) 4-amino-7-(N-tert-butoxycarbonyl-3-chlorobenzylamino)ethyl-8-chloro-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline; or

j) 4-amino-8-chloro-7-(3-chlorobenzylamino)ethyl-2,3,3a,9b-tetrahydro-1H-cyclopenta[c]quinoline dihydrochloride;

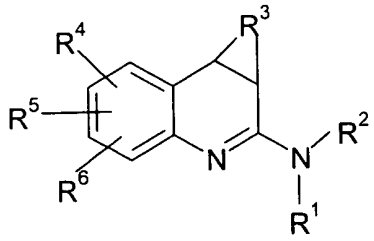
or a pysiologically compatible salt thereof.

12. A method according to claim 9, wherein the ~~neurogenerative~~ neurodegenerative disease is cerebral ischemia, hypoxia, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's Disease, Huntington's Disease, Korksakoff's Disease, epilepsy, vomiting, stress, sleep disorders, schizophrenia, depression, migraine, pain, hypoglycemia,

dementia, Alzheimer's Disease, HIV-dementia or presenile dementia.

15. A method for treating a neurodegenerative disease characterized by ~~inhibiting~~ neuronal NDS, comprising inhibiting neuronal NDS by administering an effective amount of a compound according to claim 1.

16. A compound ~~according to claims 1~~ of formula I,



(I)

wherein

R^1 and R^2 are, each independently, hydrogen or C_{1-6} alkyl,

R^3 is a saturated or unsaturated C_{1-5} alkylene radical, which is optionally substituted in 1 to 4 places with OR^7, $NR^{11}R^{12}$ or C_{1-4} alkyl and in which 1 or 2 CH_2 groups are optionally and independently replaced by O, $S(O)_n$, NR^8, =N- or carbonyl, and which are optionally bridged with a methano, ethano or propano group,

R^4 is C_{1-4} alkyl, substituted with $NR^{14}R^{15}$,

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R^8, R^{11}

and R^{12} are, independently of one another, Hydrogen, C_{1-6} alkyl, C_{6-10} aryl, which optionally is substituted with halogen or C_{1-4} alkyl, COR^{10}, CO_2R^{10}, $CONR^{18}R^{19}$ or $CSNR^{18}R^{19}$,

R^9, R^{10} and R^{20} are, independently of one another, C_{1-6} alkyl or C_{6-10} aryl, which optionally is substituted with halogen or C_{1-4} alkyl,

R^{14} and R^{15} are, independently of one another, Hydrogen, CO_2R^{20} or C_{1-6} alkyl, which optionally is substituted with halogen, hydroxy, C_{1-4} alkoxy, nitro, amino, C_{1-6} alkyl, trifluoromethyl, carboxyl, cyano, carboxamido, C_{3-7} cycloalkyl, indanyl, 1,2,3,4-tetrahydronaphthyl, C_{6-10} aryl, wherein the aryl radical is optionally substituted with halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, CF_3, NO_2, NH_2, $N(C_{1-4}$ alkyl$)_2$ or carboxyl, or

R^{14} and R^{15} optionally together with the nitrogen atom form imidazole, indole, isooxazole, isothiazole, furan, oxadiazole, oxazole, pyrazine, pyridazine, pyrimidine, pyridine, pyrazole, pyrrole, tetrazole, thiazole, triazole, thiophene, thiadiazole, benzimidazole, benzofuran, benzoxazole, isoquinoline, quinoline, furanyl, thienyl, piperidine, pyrrolidine, morpholine, thiomorpholine, hexahydroazepine, piperazine, N-methyl-piperazine, 2,6-dimethylmorpholine, phenylpiperazine, 4-(4-fluorobenzoyl)-piperidine, or indazole, and

n is 0, 1 or 2,

or a tautomeric or isomeric form or a salt of a compound of formula I.